Remarks

Reconsideration of this Application is respectfully requested.

Claims 1-40 are pending in the application, with claims 21, 30 and 40 being the independent claims. Claims 1-20 have been withdrawn.

Based on the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections under 35 U.S.C. § 112 and Claim Interpretation

The Examiner has rejected claims 30-39 under 35 U.S.C. § 112, second paragraph, asserting that they are indefinite. (OA, page 4). More specifically, the Examiner takes issue with the recitation of "wherein said DNA product contains an amount of host cell derived impurities that is undetectable by any one of a group consisting of: LAL assay, Southern blot assay, chromatography, Northern blot assay, and ethidium bromide agarose analysis." (OA, page 4.) The Examiner asserts that the detection limit of any particular assay recited in claim 30 "depends on the conditions under which it is performed as well as the ingredients used," and therefore "the level of impurities detected will depend on where and how the assay is performed." (OA, page 4). Further, the Examiner asserts that the Applicants did not specify conditions and cutoff values that would result in undetectable levels of impurities for the listed assays. (OA, page 4). Applicants respectfully traverse this rejection.

As explained in the specification of the present application, "[t]he DNA product produced by this manufacturing process is essentially free of, contains only trace levels of, or contains undetectable levels of host cell derived impurities." (Specification at

[0021].) Examples of such host cell derived impurities include, but are not limited to, RNA, protein, endotoxins, pyrogens and host chromosomal DNA. (Specification at [0021].) The specification also points out typical methods for measuring levels of DNA, RNA, protein or endotoxins: LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide agarose analysis. (Specification at [0085].)

Claims 30-39 meet the definiteness requirement of § 112 because LAL assay, Southern blot assay, chromatography, Northern blot assay and ethidium bromide agarose analysis are simply not sensitive enough to detect the amounts of impurities that may be present in the DNA product of claims 30-39, regardless of the assay conditions. Since the described methods are not sensitive enough to detect any impurities in the claimed DNA product ***under any conditions***, recitation of assay conditions in claim 30 is unnecessary because the metes and bounds of the claims as presently written would be clear to a person of ordinary skill in the art. Thus, claim 30 and any claims depending therefrom are sufficiently definite to satisfy 35 U.S.C. § 112, second paragraph. Reconsideration and withdrawal of this rejection is respectfully requested.

The Examiner asserts that the Applicants did not define the term "about X units," and therefore considers "any reasonable value below or above a given number X" to anticipate the term. (OA, page 5). Applicants respectfully disagree.

The recitation of "about" as it is used in the specification and presently-pending claims 21-40 would be understood by a person of ordinary skill in light of the technology embodied by the invention and therefore is sufficiently definite to satisfy the requirements of 35 U.S.C. 112, ¶2. *See W.L. Gore & Associates, Inc. v. Garlock, Inc.*, 721 F.2d 1540, 1557, 220 USPQ 303, 316 (Fed. Cir. 1983) ("use of 'stretching . . . at a

rate exceeding about 10% per second' in the claims is not indefinite."). Section 2173.05(b) of the MPEP states that "[i]n determining the range encompassed by the term "about", one must consider the context of the term as it is used in the specification and claims of the application," citing *Ortho-McNeil Pharm., Inc. v. Caraco Pharm. Labs., Ltd.*, 476 F.3d 1321, 1326 81 USPQ2d 1427, 1432 (Fed. Cir. 2007).

In this case, the Examiner states that "Applicants show that a standard deviation of the measurement in four samples [of endotoxin] was 100% of the measurement value, i.e. the result was 0.0001 EU/μg ± 0.0001 EU/μg of product, and for the host cell DNA levels it was 60%, *i.e.* 0.0005 μg/μg ± 0.0003 μg/μg of product," and asserts that these results do not constitute a "small margin of error. . . ." (OA page 5, internal citations omitted). Applicants respectfully disagree with this assertion.

A person of ordinary skill in the art of DNA production would understand that the use of "about" with the recited numerical ranges merely allows for the small margin of error that is associated with assays used to measure impurities using a dilution series as in the case of the LAL assay. Inherent features of the assay create slight variance associated with extremely low levels of endotoxin. In the case of host cell DNA measurements, the stated standard deviation represents a difference of 0.05% ± 0.03% of the ***total*** DNA. This translates to an extremely small difference in proportion to the total isolated DNA of interest. Reconsideration and withdrawal of this rejection is respectfully requested.

Thus, the Examiner's assertion that "any reasonable value below or above a given number X is considered to anticipate this term based on the use of "about" expands the scope of the term well beyond its meaning as understood by a person of ordinary skill in

the art. More specifically, in light of the specification and claims, a person of ordinary skill in the art would understand "about X units," where X is included in a dilution series range, to encompass $\geq$ X where X defines the lower limit of the dilution series range and $\leq$ X when X defines the higher limit of the dilution series range as measured by a positive result between two samples in a dilution series. In the present case, LAL analysis, which is used for measuring endotoxin levels, uses dilution series methodolgy. Thus, Applicants assert that the scope of "about" with regard to the endotoxin ranges recited in the presently-pending claims would be understood to account for in accuracies associated with dilution series methodology.

The Examiner also asserts "[a]s the amounts of RNA and protein claimed are extremely small as well, it is reasonable to assume that the measurement error would be of the same order. . ." (OA, page 5). Applicants respectfully disagree. Contrary to the standard assay for measuring endotoxin levels, such as the LAL assay discussed above, assays available for measuring protein and RNA levels are highly quantitative. For example, quantitative Northern blot analysis (for RNA) and HPLC (for amino acid levels) are highly precise assays. Therefore, Applicants assert that it is incorrect for the Examiner to assume that variance of the levels RNA and amino acids would be comparable to that of endotoxin given the different nature of the assays used to detect the respective components. Further, Applicants assert that a person of ordinary skill in the art would take into consideration the accepted methods for measuring protein and RNA levels and would therefore understand the term "about" recited in reference to these levels to allow for a margin of error appropriate for each accepted method. Accordingly, Applicants assert that the meaning of "about" as it is used in presently-pending claims

30-39 is sufficiently definite to satisfy 35 U.S.C. § 112, ¶2. Reconsideration and withdrawal of this rejection is respectfully requested.

Rejections under 35 U.S.C. § 102

The Examiner has rejected claims 30-39 under 35 U.S.C. § 102(b) over U.S. Patent Application Publication No. 2001/0034435 A1 ("Nochumson *et al.*"). (OA, page 5.) The Examiner asserts that Nochumson *et al.* teach a plasmid DNA and pharmaceutical preparation that anticipates the ranges recited in claims 30-39. (OA, page 5.) More specifically, the Examiner asserts that on page 8, [0099] of the published application, Nochumson *et al.* teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA, plasmid DNA preparations with 0.05% of host DNA (equivalent to 0.0005 μg of host DNA/μg of DNA product), less than 0.06% of protein (equivalent to 0.0006 μg/μg of DNA product), and less than 0.2EU/mg of endotoxin (equivalent to less than 0.0002 EU/μg). The Examiner concludes that Nochumson *et al.* anticipate the ranges recited in claims 30-39 of the present application. (OA, page 4). Applicants respectfully traverse this rejection.

Since the range of contaminants taught by Nochumson *et al.* were detected and calculated, by definition they were ***not*** undetectable, and thus, they cannot, by definition, anticipate the undetectable (by the recited methods) amounts of impurities in the DNA product of claims 30-39. Accordingly, Nochumson *et al.* do not disclose the claimed invention and cannot anticipate the claims under § 102(b). Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejections under 35 U.S.C. § 103

The Examiner has rejected claims 21-29 and 40 under 35 U.S.C. § 103(a) over Nochumson *et al*, U.S. Application Publication No. 2003/0109696 A1 ("Kvederas.") and Cooke *et al.* (J. Biotechnol., vol. 85, pp. 294-304. February 2001)("Cooke"), asserting, *inter alia*, that Nochumson *et al.* teach plasmid DNA preparation with 95% plasmid DNA and less than 5% RNA. (*See* OA, page 5). The Examiner also asserts that Kvederas *et al.* teach a method of 100% removal of bacterial RNA from a preparation of plasmid DNA derived from bacterial cells, citing the Abstract; page 14,15, Tables 3 and 4. (*See* OA, pages 7-8.) The Examiner also asserts that the motivation to remove RNA from the plasmid preparation would have been provided by Kvederas *et al.* (page 1, 0005) and Cooke *et al.* (page 298, second paragraph). Additionally, the Examiner asserts that Cooke *et al.* teach removal of RNA from plasmid preparations using host cells expressing a ribonuclease. (*See* OA, page 8.) Applicants respectfully traverse this rejection.

In order to establish a *prima facie* case of obviousness, the proper analysis is to first consider whether the following three criteria are met: (1) there must be some reason, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings; (2) there must be a reasonable expectation of success; and (3) the prior art reference (or references when combined) must teach or suggest all the claim limitations. MPEP § 2143.

In this case, the Examiner has failed to present a *prima* facie case of obviousness for presently-pending claims 21-29 and 40 because the cited references, alone or in

combination, do not teach each and every element of the rejected claims. Additionally, even if the cited references were to teach each and every element of claims 21-29 and 40, they fail to provide a reasonable expectation of success in arriving at the DNA product of the presently-pending claims. Furthermore, the cited references actually provide evidence of a long-felt need for a purified DNA product, that is satisfied only by the presently-claimed invention. Such a long-felt, but unsatisfied need is evidence of non-obviousness. *See Graham v. John Deere Co.,* 383 U.S. 1 (1966).

Contrary to the Examiner's assertion, Kvederas *et al.* do not teach a method of plasmid DNA purification from bacterial cells which results in a 100% removal of bacterial RNA from the preparation (final RNA concentration is 0%). More specifically, tables 3 and 4 of the Kvederas *et al.* reference show milligram quantities of RNA remaining at various process steps, but tables 3 and 4 do not contain data regarding the level of RNA contamination in the final DNA product. (*See* Kvederas *et al.* Tables 3 and 4, Column "RNA amount, mg".) Applicants specifically note the blank space in the "RNA amount, mg" column in the final row and respectfully assert that leaving a blank space in a table is not the same as showing 100% of the contaminating RNA was removed. Further, Applicants would like to bring the Examiner's attention to paragraph [0126] of the Kvederas *et al.* reference which states "the final RNA amount in the plasmid DNA solution after [the] Fine [*sic*] RNA removal step at 50°C temperature constituted only about 1% of the total absorption at 260 nm," which shows that RNA contamination was not at 0%. Finally, Kvederas *et al.* repeatedly characterized their process as removing "***substantially*** all RNA," as opposed to complete removal of RNA. (Kvederas *et al.*, abstract, [0028], [0087], [0088] (emphasis added)). Thus, Kvederas

does not teach a method of plasmid DNA purification that results in a final RNA concentration of 0% or even an amount that is within the RNA range recited in claims 21-29. In fact, the inability of Kvederas *et al.* to remove 100% RNA from the DNA product demonstrates the long-felt need for efficient, inexpensive removal of contaminating RNA discussed in paragraphs [0006-0008] of the present specification, which is satisfied by the presently-claimed DNA product. Long-felt and unsatisfied need is an objective indication of non-obviousness that must be considered in the Examiner's analysis. *See Graham v. John Deere Co.,* 383 U.S. 1, 17-18 (1966); *see also Ruiz v. A.B. Chance Co.*, 234 F.3d 654, 667 (Fed. Cir. 2000)("Our precedents clearly hold that secondary considerations, when present, must be considered in determining obviousness.")

Additionally, even if Kvederas *et al.* reported that they were unable to detect RNA in their DNA product, that would not be persuasive evidence of total RNA removal because they did not use methods or equipment appropriate for a quantitative determination of RNA contamination levels. Kvederas employs low pressure chromatography (HiTrap Q HP column) and gel analysis to quantitate polysaccharides, host cell protein and host cell DNA contaminant content. The HiTrap column is not an analytical column and is not intended to be used for this application. Instead, specific assays are recognized in the art to be required to accurately and reproducibility conduct quantitative analysis of these contaminants: For example, southern blot analysis for host cell DNA and BCA or amino acid analysis are used for quantitative analysis of proteins. HPLC should be used to accurately determine % supercoiled and open circular DNA.

There are two methods that are standard in the art for detecting RNA: agarose gel (which is employed by Kvederas) and Northern blot analysis. Agarose gel analysis has extremely limited sensitivity because the limit of detection for RNA by agarose gel analysis is approximately 12.5 ng. Thus, ascertaining complete elimination is not possible by this method. Only with a Northern blot using specific probes against the host RNA can one quantitate very low levels in the picogram to femtogram range of RNA . The DNA product claimed in presently-pending claims 21-40 is below the quantitative limits, *i.e.*, undetectable by agarose gel analysis. Accordingly, the DNA product disclosed by Kvederas *et al.* is not within the scope of presently-pending claims 21-40.

Despite the fact that the Examiner admits that Nochumson *et al.* do not teach RNA contaminant levels of 0.00001% to 0.0001%, the Examiner asserts that combining Nochumson *et al.* and Kvederas *et al* would have provided a person of ordinary skill in the art at the time of filing with a reasonable expectation of success in producing a DNA product with 0.00001% to 0.0001% RNA as required in claims 22 and 23.(*See* OA p. 8.) For the reasons discussed above, Applicants assert that a person of ordinary skill in the art would have encountered the same difficulties experienced by Nochumbson *et al.*, Kvederas *et al.* and Cooke *et al.* in DNA purification and therefore would not have had a reasonable expectation of success in arriving at the DNA product of presently-pending claims 21-40.

The Cooke *et al.* reference cited by the Examiner provides additional proof of long-felt need for the presently-claimed DNA product. More specifically, the Examiner cites Cooke *et al.* as teaching removal of RNA from plasmid preparations using host cells expressing a ribonuclease and for the recognition that RNA contamination can

cause potentially lethal complication in patients. (*See* OA, page 8.) The excerpt cited by the Examiner ignores other problems associated with DNA product produced by the method disclosed by Cooke *et al.* More specifically, a person of ordinary skill in the art at the time of filing would have known that obtaining a DNA product free of RNA by use of a ribonuclease, as disclosed by Cooke *et al.*, would be undesirable if the DNA product was to later be used in a pharmaceutical setting, since commercially available ribonuclease is derived from xenogenic sources that possibly contain contaminants. Thus, Cooke *et al.* provide further evidence of the long-felt, but unsatisfied need for the DNA product of the present invention discussed above.

The Examiner has also rejected claims 24 and 27 under 35 U.S.C. § 103(a) over Nochumson *et al.* Specifically, the Examiner asserted that Nochumson *et al.* teach plasmid DNA preparation with 0.05% of host DNA, which allegedly anticipates the limitations of about 0.00004 and of about 0.0005 μg of host DNA/μg of DNA product. Neither of claims 24 and 27 is obvious over Nochumson *et al.* for the reasons discussed above. Additionally, a preparation with 0.05% of host DNA does not fall within the scope of claim 24, because 0.00004 μg host DNA/μg of DNA product, as recited in claim 24, is a full order of magnitude lower than the alleged teaching of 0.05% host DNA.

Applicants respectfully assert that the reference cited by the Examiner do not teach or suggest each and every element of the presently-pending claims. The Examiner also has not shown a reasonable expectation of success in arriving at the claimed invention based on the disclosure of Nochumson *et al.*, Kvederas *et al.* or Cooke *et al.* Applicants respectfully assert that a *prima facie* case of obviousness has not been made

with respect to the current claims, and therefore request that the Examiner reconsider and withdraw this rejection.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

STERNE, KESSLER, GOLDSTEIN & FOX P.L.L.C.

for Elizabeth J. Haanes #42,613

Laura A. Vogel
Attorney for Applicants
Registration No. 55,702

Date: October 20, 2008

1100 New York Avenue, N.W.
Washington, D.C. 20005-3934
(202) 371-2600

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